Drug Approval Process Application Integrity Policy Citizen Petition

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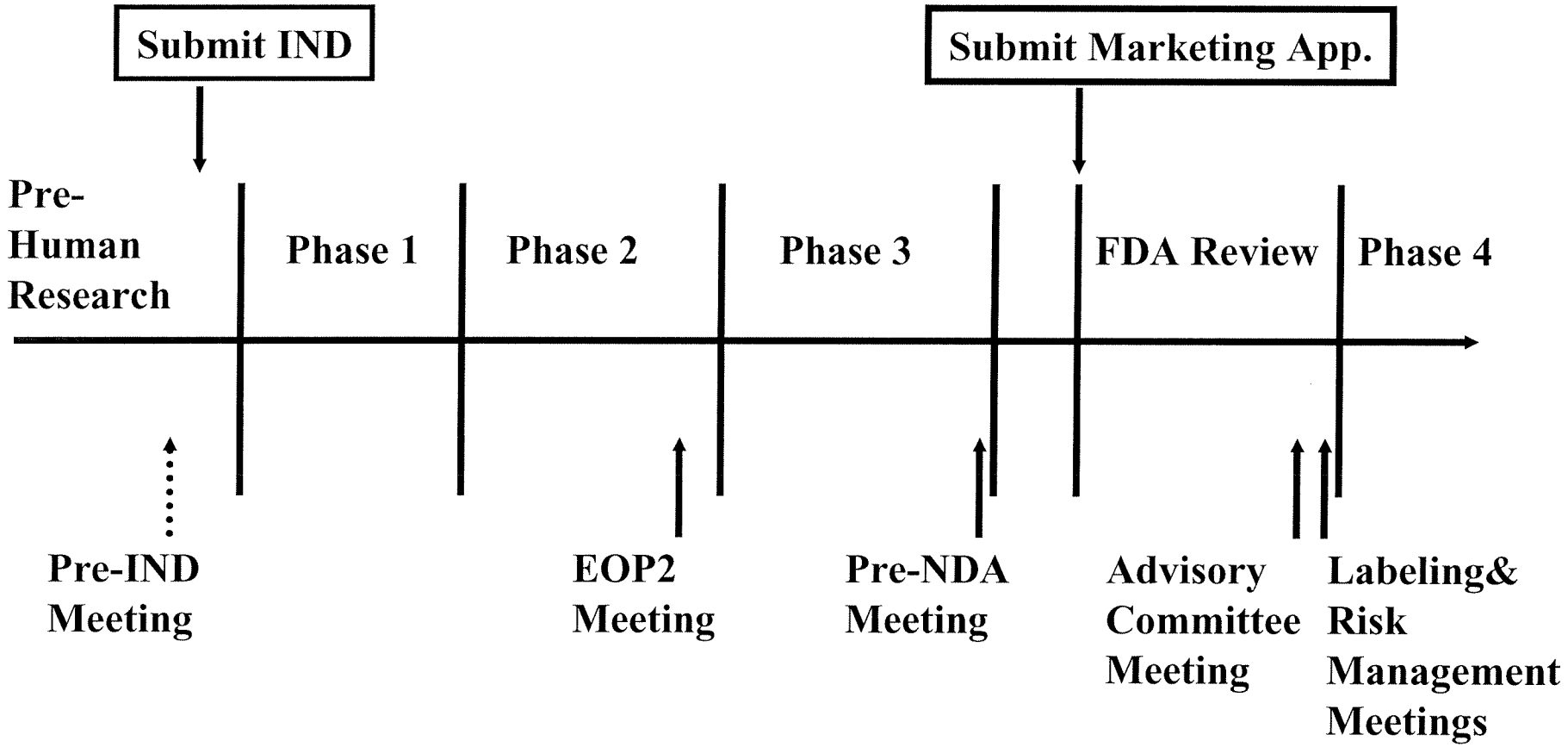
Acronyms

- IND= Investigational New Drug Application
- NDA= New Drug Application
- BLA= Biologic License Application
- AIP= Application Integrity Policy
- CP= Citizen Petition

Drug development and review –



Marketing application: content

- Chemistry and manufacturing information: ensure the identity, strength, quality, and purity of the drug
- Nonclinical information: studies in animals as they relate to drug's proposed therapeutic indication
- Microbiology information: demonstration of effect on bacteria or viruses

Marketing application: content

- Clinical information: studies in humans
  - How the drug acts in the body
  - What happens to the drug in the body
  - Studies to find the right dose
  - Studies to demonstrate effectiveness and safety
- Statistical analyses

Scope of clinical information

- Controlled clinical trials pertinent to proposed use
- Uncontrolled clinical trials
- Other data/info relevant to evaluation of safety & effectiveness
  - Studies in other uses
  - Commercial marketing experience
  - Published reports
  - Unpublished scientific papers

Integrated Analyses

- Integrated Summary of Effectiveness
  - For proposed use
  - Dosage and administration
  - Demographic analyses
  - Analyses in special populations

Integrated Analyses

- Integrated Summary of Safety
  - All available information on safety (including pertinent animal data)
  - Demonstrated or potential adverse effects
  - Interactions with other drugs
  - Data from epidemiological studies of related drugs
  - Analyses by demographics
  - Analyses in special populations

Multidisciplinary Review Team

- Physician
- Chemist & manufacturing expert
- Nonclinical pharmacologist/toxicologist
- Clinical pharmacologist/toxicologist
- Statistician
- Project Manager
- Microbiologist

Extended Team

- Safety evaluator (Office of Surveillance and Epidemiology)
- Compliance investigators
  - Manufacturing facilities
  - Clinical site audits
- Consultants (input on specialty topics)
  - Internal
  - External

Drug Review Process

- Filing review
  - Application complete for review?
  - Review priority?
  - Any consults needed?
  - Advisory committee meeting?
- Requests for additional information
- Review
  - Primary review
  - Team Leader review
  - Signatory authority review

Drug Review Process

- Advisory Committee meeting (as needed)
- Decision
  - Insufficient information- sponsor is informed of deficiencies
  - Benefits outweigh risks for intended use as described in labeling- approval

Benefit/Risk Ratio

- Severity of disease
- Efficacy of existing therapies
- Can change over time as more is learned about the drug
- FDA evaluates risks for the population
- Healthcare provider evaluates risks for a patient
- A patient evaluates risks in terms of personal benefits

Special Programs for Review

- Accelerated approval
  - Approval based on a surrogate endpoint for clinical benefit
  - Approval with marketing restrictions to assure safe use
- Review priority
  - Priority (no alternatives, significant advance): 6 month time frame to action
  - Standard: 10 month time frame to action
- Fast Track: use in life-threatening or seriously debilitating disease or condition

Changes to an Approved Application

- Types of changes
  - Manufacturing
  - Formulation
  - New strength
  - New dosage form
  - New indication, claim, or use
  - Switch from Rx to OTC marketing
  - Labeling revisions (e.g., new safety warning)
- Supplemental application
- New original application

Postmarketing Surveillance

- Reports of adverse drug experiences that are both serious and unexpected ("15-Day Alert Reports")
  - Foreign and domestic
  - Commercial marketing experience
  - Postmarketing clinical investigations
  - Postmarketing epidemiological/surveillance studies
  - Scientific literature
  - Unpublished scientific papers

Postmarketing Surveillance

- Periodic adverse drug experience reports
  - Experiences not reported as "15-Day Alert Reports"
  - Analysis of "15-Day Alert Reports" for past year
  - Quarterly for 3 years after approval
  - Annually thereafter

Application Integrity Policy (AIP)

- "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities"- Final Policy (Federal Register, 56 FR 46191)
- Focus- integrity of data and information in applications submitted to FDA for review and approval

Invoking the AIP

- Evidence of pattern or practice of wrongful conduct that raises significant question about the reliability of data
- AIP invoked
  - Usually invoked when $\geq$2 applications affected
  - 1 application- data integrity issues resolved through review process unless review process inadequate to deal with the integrity issue

AIP Invoked

- Review stops on all affected applications
- Independent internal review
- Corrective Action Plan
- Validity review (compliance)
- Outcome
  - Application withdrawn by sponsor
  - FDA withdrawal of approval
  - Recall of drug from market
  - Seizure, injunction, civil penalties, criminal prosecution
  - AIP Revoked